CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA 06-02: CIRM COMPREHENSIVE RESEARCH GRANT PROGRAM

The goal of the California Institute for Regenerative Medicine (CIRM) is to develop stem cell and related research for the diagnosis, prevention and treatment of disease and injury. Toward that end, CIRM plans to fund a broad and varied program of stem cell research and training, and is currently developing a scientific strategic plan to guide this program. An unexpected development, however, has made funds immediately available that can be used to fund stem cell research before the strategic plan is completed. These funds will be focused on the greatest immediate need, which is research on human embryonic stem cells (hESCs). At a later time, CIRM will offer opportunities for funding across a broader range of projects.

The first CIRM research grant initiative, *Innovation in Human Embryonic Stem Cell Research*, is intended to "jump-start" human embryonic stem cell research in California. It will be carried through three Requests for Applications (RFAs), two for individual investigator projects and one for institutional shared laboratory space:

RFA 06-01: CIRM SEED Grants
RFA 06-02: CIRM Comprehensive Grants
RFA 06-03: CIRM Shared Research Laboratory Grants and Stem Cell Techniques Course

The CIRM Comprehensive Research Grant RFA is the second of these three.

OBJECTIVE OF THE CIRM COMPREHENSIVE RESEARCH GRANT PROGRAM – RFA 06-02

The objective of this solicitation of the Comprehensive Research Grants Program is to support mature, ongoing studies on hESCs by scientists with a record of accomplishment in this field. This is also an opportunity for investigators with well-developed expertise in hESC research or in a closely-related stem cell field to expand their programs or take promising new directions in hESCs research based on current research. In their application, the Principal Investigator (PI) is expected therefore to provide strong preliminary data to demonstrate feasibility and the promise of the proposed research. PIs may be either senior or junior faculty and must be full-time employees of the grantee organization.

This RFA is open to all academic and non-profit research institutions in California. Future solicitations may be available to for-profit institutions when the CIRM Intellectual Property Policy for for-profit organizations is in place. CIRM also wishes to attract new investigators - young investigators as well as established scientists in other fields - to direct their focus to hESC research. They are encouraged to apply for SEED (Scientific Excellence through Exploration and Development) grants (RFA 06-01), designed to support studies that may yield preliminary data and/or proof of principle that could then be extended to full scale investigations. Unlike Comprehensive Research Grant

applications, SEED Grant applications are not required nor expected to have preliminary data. Investigators may apply for either a SEED grant or a Comprehensive Research grant as a PI, **but not both**. CIRM will accept only **one application** per Principal Investigator (PI) for one or the other RFA.

KEY FEATURES OF THE CIRM COMPREHENSIVE GRANT PROGRAM

This solicitation is limited to proposals that work directly on hESCs and that can utilize existing space and major equipment at the applicant institution. Funding will be provided for Project costs and other related costs as described in the CIRM Grants Administration Policy (http://www.cirm.ca.gov/policies/pdf/InterimGAP.pdf). Project costs of up to $400,000 per year for up to 4 years may be requested. The allowable Indirect Costs for this RFA are limited to 25% as described in the CIRM Grants Administration Policy (GAP).

This solicitation is not targeted to any specific aspect of hESC research or to a particular disease. Topics for investigation should be chosen solely for their potential to add substantially to the body of knowledge on hESCs or to develop a useful research tool or to develop therapy. Future solicitations may be limited to research on topics to be identified through the Institute's scientific strategic planning process and published as its highest priorities for funding.

The following are examples of hESC research that are expected to be encompassed within this RFA; applications for other innovative projects will also be considered and are strongly encouraged.

- Development of new technology and conditions to optimize the derivation, self-renewal, maintenance, stability, cryopreservation of hESCs.
- Derivation of disease-specific hESC lines
- Characterization and comparison of different hESC lines.
- Understanding the regulation of self-renewal and fate decisions
- Targeting lineage-specific differentiation of hESCs
- Assessing the fates of hESCs and their derivatives in animal models of disease
- Assessing the tumorigenicity of hESCs and their derivatives.
- Reprogramming of adult human somatic cell nuclei or other new techniques to generate hESCs.

FUNDS AVAILABLE

CIRM intends to commit up to $80 million over a four year period for this RFA. The Institute anticipates that approximately 25 Comprehensive Research Grants will be awarded for no more than a period of four years each. CIRM reserves the right to discontinue or change funding levels from year to year if significant scientific progress is not demonstrated.

ELIGIBLE COSTS

All allowable costs for research grants are detailed in the CIRM Grants Administration Policy (http://www.cirm.ca.gov/policies/pdf/InterimGAP.pdf).

1. **Salaries for key personnel** providing services to the grant. This may include the Principal Investigator, research associate, and/or technical support salaries, based on percent of full time effort commensurate with the established salary structure of the applicant institution. Because CIRM considers pre-doctoral, post-doctoral and clinical fellows as trainees and not as employees, institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries are expected to be covered by the Indirect Costs for the grant.

2. **Equipment and Supplies** Major equipment necessary to conduct the research proposed must already be available at the applicant institution (see definition of equipment in the CIRM GAP). Minor equipment purchases (< $5,000 per item) may be included in the budget. Supplies, including specialized reagents and animal costs may also be purchased with grant funds.

3. **Travel** Recipients (PIs) of CIRM Comprehensive Research Grants are expected to attend an annual CIRM-organized meeting in California and should include in the budget costs for travel to this meeting. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the CIRM GAP.

APPLICATION PROCEDURE

Letter of Intent

All institutions and investigators planning to apply for a CIRM Comprehensive Research Grant must notify CIRM with a letter of intent (LOI) by **September 15, 2006**. Please use the template for the (LOI) provided at (http://www.cirm.ca.gov/funding/pdf/LOI.pdf). The letter should describe concisely the overall goals of the proposed research and technical approaches used to achieve these goals. Include a list of proposed out-of-state collaborators; if collaboration with other Californian institutions is planned, this information should also be included. If collaboration with other institutions is planned, this should also be included. In order to facilitate planning for the review of the application, please identify the types of expertise needed to evaluate the proposal. Letters of intent are non-binding, but applications will not be accepted if such a letter has not been provided by the deadline. Letters of intent can be sent as an email attachment to loi@cirm.ca.gov.

Full Application Instructions

All applications for Comprehensive Research Grants must be received by **November 13, 2006**. Only applicants who have sent in an LOI will be allowed to submit an

application. Applicants must use the CIRM Comprehensive Research Grant Application Form which will be available on the CIRM website by September 15, 2006.

The application for Comprehensive Research Grants includes:

- Abstract (up to 3000 characters): State the goals of the proposal; summarize the overall plans of the research proposed and how it will meet the stated objectives of the proposal. Describe the rationale for these studies and techniques you will use to pursue these goals. Explain the likelihood of this proposal being funded by the federal government.

- Public Abstract (up to 3000 characters): Briefly describe in lay language the proposed research and how it will, directly or indirectly contribute to the development of diagnostic tools or therapies. This Public Abstract will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant (PI and home institution).

- Statement of Benefit to California (up to 3000 characters): Describe in a few sentences how the proposed research will benefit the state of California and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant (PI and home institution).

- Specific Aims (up to 1 page): Explain the broad, long-term objectives and the goal of the specific research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology. Identify and enumerate each specific aim of the proposal, in a concise and step-wise fashion, and how that will lead to the broad goal of this research. Explain the likelihood of this proposal being funded by the federal government.

- Rationale and Significance (1-2 pages): Summarize the context of and background leading to the present application and the specific rationale for the exploratory work proposed. Evaluate existing knowledge and specifically identify the gaps that the project is intended to fill. State how the proposed research meets CIRM's goals of funding innovative, perhaps scientifically risky research. If the aims of the application are achieved, state how this information will lead to further research that will add substantially to the body of knowledge on hESCs or to the development of diagnostics and/or therapies based on stem cell research.

- Research Design and Methods (up to 5 pages): Describe concisely, but in sufficient detail to permit evaluation of the merit of the research, the experimental design, methods and techniques to be employed to achieve the goals specified in the proposal. Identify the new or risky aspects of the research, the anticipated pitfalls, and plans to overcome or circumvent difficulties that may arise. Describe the methods of analysis of results, including criteria for success of the preliminary studies.

- Preliminary Results and Feasibility (up to 4 pages): Provide preliminary data to support the concepts, hypotheses and/or approaches proposed in the application. Provide any information that will help to establish the experience and competence of the investigator to pursue the proposed project. Does the investigator have access to appropriate technology to perform the research?

- Collaboration (up to 1 page): If collaboration is integral to the success of the project, describe exactly how this will be achieved.

- Timeline (1/2 page): Provide a realistic timetable for completing each proposed specific aim of the project; where appropriate provide specific milestones for evaluating the achievement of each specific aim.

- References (up to 3 pages): List all references used in the body of the proposal.

- Laboratory/Clinical Facilities including major equipment (up to 1 page): Provide a short description of the facilities and environment in which the work will be done, and the major equipment and resources available for conducting the proposed research. Discuss ways in which the proposed studies will benefit from unique features of the scientific environment or employ useful collaborative arrangements where applicable.

- Key Personnel: List the scientific participants and their roles in the proposed research, regardless of whether they will receive salary support from the grant. These may include the Principal Investigator, co-investigators, research associates, technicians and trainees (students and fellows). For each key scientific personnel listed, provide a 2 page biographical sketch that highlights prior stem cell (especially hESC) research experience and/or special skills related to the proposed research. Include relevant publications.

- Budget: Provide all budget information requested in the budget section of in the application form.

REVIEW AND AWARD PROCESS

CIRM Comprehensive Grant applications will be reviewed by the Scientific and Medical Research Funding Working Group (SMRFWG) of CIRM. The SMRFWG consists of fifteen basic and clinical scientists from institutions outside California, seven patient advocates who are members of the Independent Citizen's Oversight Committee (ICOC), and the Chair of the ICOC. The membership of the SMRFWG can be viewed at: http://www.cirm.ca.gov/working_group/pdf/GrtWkgGpMbr.pdf. The ICOC was established by the California Research and Cures Act (Proposition 71) to oversee CIRM and makes all final funding decisions. The composition of the ICOC van be viewed at: http://www.cirm.ca.gov/icoc/pdf/Members.pdf.

Fifteen scientists on the SMRFWG will review the applications and rate them according to scientific and technical merit. The following are among the qualities to be considered for evaluation of research grant applications. For Comprehensive Research Grants,

particular emphasis will be placed on impact and significance and quality of the research plan.

- **Impact and Significance** Does the research address an important problem? Will the proposed research significantly move the field forward, either scientifically or medically?

- **Quality of the Research Plan** Is the research carefully planned to give a meaningful result? Are the possible difficulties acknowledged, with alternative plans should the proposed strategy fail? What is the timetable for achieving such significant results?

- **Innovation** Is the approach original? Does it bring novel ideas, technologies or strategies to bear on an important problem? Does it break new ground?

- **Feasibility** Are the preliminary data compelling and support the concepts, hypotheses and approaches proposed in the application? Can the aims of the research by reasonably achieved? Does the investigator have access to appropriate technology to perform the research?

- **Investigators** Do the investigators have the training and experience to conduct the proposed project?

- **Collaboration** Does the proposal support collaborative efforts, and if so, to what extent do the collaborations enhance the quality and potential of the research proposed?

- **Responsiveness to the RFA** How is the proposal responsive to the criteria and objectives stated in the RFA?

- **Eligibility for Federal funding** Is the research ineligible or unlikely to receive Federal funding? If not, is the research sufficiently compelling in that it presents "a vital research opportunity" that will materially aid the objectives of CIRM?

Recommendations for funding will then be made by the full SMRFWG to the ICOC. In making these recommendations, the SMRFWG will review the entire portfolio of applications, taking into consideration the following criteria:

- Scientific and technical merit.

- Appropriate balance between innovation and feasibility.

- Where relevant, the appropriate balance between fundamental research, therapy development and clinical application.

- Where relevant, the appropriate balance and range of diseases addressed.

- Other considerations from the perspective of patient advocates.

SUBMITTING AN APPLICATION

All Comprehensive Research Grant applications must be submitted to CIRM by **November 13, 2006**. The application form for CIRM Comprehensive Research Grants will be available on the CIRM website by September 15, 2006. Send a PDF file of the full application to Comprehensive@cirm.ca.gov. In addition to submitting the application electronically, send a signed original of the completed application to CIRM. The hardcopy must be signed by both the PI and the institution's authorized organizational official. Mail the signed hardcopy to:

Comprehensive Grant Application
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

RECEIPT AND ANTICIPATED REVIEW AND START DATES

Receipt of letters of intent:	September 15, 2006
Receipt of full application:	November 13, 2006
Review of applications:	January, 2007
Review by ICOC:	March-April, 2007
Announcement of awards:	March-April, 2007
Earliest funding of awards:	April-May, 2007

Contact Information

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OTHER REQUIREMENTS

CIRM Grants Administration Policy:

CIRM's governing board, the ICOC adopted an Interim Grants Administration Policy (GAP) for Academic and Non-profit Institutions that serves as the standard terms and conditions of grant awards issued by the Institute. All research conducted under this award will be expected to comply with the stated policy, which can be found on the CIRM website at http://www.cirm.ca.gov/policies/pdf/InterimGAP.pdf. Funding from year to year will depend on scientific progress achieved.

Human Stem Cell Research Regulations:

CIRM has adopted medical and ethical standards for human stem cell research. All research conducted under this award will be expected to comply with these standards which can be viewed at:
http://www.cirm.ca.gov/laws/pdf/Proposed_Interim_Guidelines_ICOC_Modified.pdf
While these regulations prohibit donors of gametes, embryos, somatic cells or human tissue from receiving valuable consideration for their donation, they do allow for reimbursement for permissible expenses as determined by an IRB. "Permissible Expenses" means necessary and reasonable costs directly incurred as a result of donation participation in research activities and may include costs such as those associated with travel, housing, child care, medical care, health insurance and actual lost wages. For research activities proposing to obtain gametes, embryos, somatic cell or human tissue from human subjects, CIRM requires the applicant to submit, at the time of application, their reimbursement policy describing how they intend to calculate permissible expenses.

Intellectual Property Policy for Non-profit Organizations:

CIRM has adopted policies that govern the intellectual property created under grant awards issued by CIRM to non-profit organizations. Research conducted under this award will be expected to comply with the terms and conditions stated in this policy which can be viewed at: http://www.cirm.ca.gov/policies/pdf/IPPNPO.pdf.